



**European Organisation for Research and Treatment of Cancer consensus  
recommendations for the treatment of mycosis fungoides/Sézary syndrome  
Update 2017**

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## Review

# European Organisation for Research and Treatment of Cancer consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome – Update 2017



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**Abstract** In order to provide a common standard for the treatment of mycosis fungoides (MF) and Sézary syndrome (SS), the European Organisation for Research and Treatment of Cancer–Cutaneous Lymphoma Task Force (EORTC-CLTF) published in 2006 its consensus recommendations for the stage-adapted selection of management options for these neoplasms. Since then, the understanding of the pathophysiology and epidemiology of MF/SS has advanced, the staging system has been revised, new outcome data have been published and novel treatment options have been introduced. The purpose of the present document is to update the original recommendations bearing in mind that there are still only a limited number of controlled studies to support treatment decisions for MF/SS and that often treatment is determined by institutional experience and availability.

This consensus on treatment recommendations was established among the authors through a series of consecutive consultations in writing and a round of discussion. Recommended treatment options are presented according to disease stage, whenever possible categorised into first- and second-line options and supported with levels of evidence as devised by the Oxford Centre for Evidence-Based Medicine (OCEBM).

Skin-directed therapies are still the most appropriate option for early-stage MF, and most patients can look forward to a normal life expectancy. For patients with advanced disease, prognosis is still grim, and only for a highly selected subset of patients, prolonged survival can be achieved with allogeneic stem cell transplantation (alloSCT). There is a high need for the development and investigation in controlled clinical trials of treatment options that are based on our increasing understanding of the molecular pathology of MF/SS.

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## 1. Introduction

Cutaneous T-cell lymphomas (CTCLs) are a group of rare non-Hodgkin lymphomas (NHLs) characterised by initial localisation of malignant T-lymphocytes to the skin. Current definition of these neoplasms follows the 2016 revision of the World Health Organisation (WHO) classification of tumours of haematopoietic and lymphoid tissues that largely incorporates the WHO-EORTC classification for cutaneous lymphomas published in 2005 (Table 1) [1,2]. The most common form among CTCLs is mycosis fungoides (MF), accounting for around 55% of cases. Sézary syndrome (SS) is much rarer making up only approximately 5%. A recent analysis by the Surveillance, Epidemiology and End Results (SEER) program of the United States National Cancer Institute (NCI) demonstrated an incidence rate of MF of about 5.6 per million persons, which has remained stable since 1995 after an increase in prior years; this may be attributed to improvement in diagnostic accuracy [3].

The clinical presentation of MF is manifold with early stages presenting with limited patches and plaques suspicious only to the experienced physician and late stages characterised by severe disease presenting with tumours, ulceration, systemic involvement and death. A number of clinical variants of MF have been described of which folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin are separately mentioned in the WHO-EORTC classification due to distinctive clinicopathological features and biological behaviour [1]. SS

is pathologically and clinically closely related to MF and defined by the occurrence of erythroderma, lymphadenopathy and leukaemic involvement. Since the initial description of MF ascribed to Jean-Louis Alibert in 1806 and of SS to Albert Sézary in 1938, both from the Hôpital Saint Louis in Paris, a number of therapeutic options have been introduced ranging from topical steroids to cytostatic chemotherapy and more recently also molecular targeted approaches [4–7]. However, due to the fact that in MF/SS the majority of available treatments are rarely able to induce long-term remissions, and according to the results of an early seminal study it is still a paradigm that treatment of patients with MF/SS is palliative and should follow a stepwise, stage-adapted approach [8]. The rare exceptions to this are allogeneic stem cell transplantation (alloSCT) in advanced disease and the anecdotal patient with long-term remission after skin-directed therapy (SDT) in early stages. These facts together with the want of evidence from larger prospective trials in an orphan disease has supported a need for the development of consensus statements by various national and international groups in which published evidence is integrated with expert opinion to provide the best available support for decision making in clinical practice [6,7,9–12]. It was with this intention that in 2004 the Cutaneous Lymphoma Task Force of the EORTC (EORTC-CLTF) embarked on an international attempt to establish consensus recommendations for the treatment of MF/SS with a special emphasis on treatment availability and access in Europe that were eventually published in 2006 [9]. As, in the meantime,

Table 1  
Classification of cutaneous T-cell lymphomas [1,2,180].

Cutaneous T-cell and NK-cell lymphoma	ICD-O-3 (morphology)
Mycosis fungoides (MF)	9700/3
MF variants and subtypes:	
Folliculotropic MF	
Pagetoid reticulosis	
Granulomatous slack skin	
Sézary syndrome (SS)	9701/3
Adult T-cell leukaemia/lymphoma (ATLL)	9827/3
Primary cutaneous CD30-positive lymphoproliferative disorders:	
Primary cutaneous anaplastic large cell lymphoma	9718/3
Lymphomatoid papulosis	9718/1
Subcutaneous panniculitis-like T-cell lymphoma	9708/3
Extranodal natural killer/T-cell lymphoma, nasal type	9719/3
Hydroa vacciniforme-like lymphoproliferative disease	9725/3
Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)	9709/3
Primary cutaneous $\gamma/\delta$ T-cell lymphoma	9726/3
Primary cutaneous CD4+ small/medium T-cell lymphoproliferative disorder (provisional)	9709/3
Primary cutaneous acral CD8+ T-cell lymphoma (provisional)	9709/3
Primary cutaneous peripheral T-cell lymphoma, unspecified	9709/3

our understanding of MF/SS pathophysiology and prognostic parameters has improved, the original tumour-node-metastasis classification (TNM) system of staging has been updated and revised, and additional treatment options have been developed; an update to this collaborative effort has become timely and is presented in the following.

## 2. Development process of recommendations

The process to revise the published EORTC consensus recommendations for the treatment of MF/SS was initiated in October 2014. Original authors and additional experts were contacted by e-mail, and comments and suggestions for update to the original recommendations were collected. This was followed by an interactive discussion at an EORTC Groups Annual Meeting (EGAM) in March 2015 and a further final collection of feedback by email. Thus current ‘best practices’ from each national group were summarised and discussed until a unanimous consensus on first and second line therapies for each disease stage was established. Since the order of options is largely based on

availability and institutional experience it was not included in the consensus development process. As in the previous document the recommendations are presented by disease stage and accompanied by ‘levels of evidence’ to facilitate interpretation.

These recommendations were developed without external funding. Individual authors’ potential conflicts of interest are disclosed in a separate section at the end of the article.

## 3. Levels of evidence

Revised Levels of Evidence have been published by The Oxford Centre for Evidence-Based Medicine (OCEBM) in 2011 and will be used in this article (Table 2) [13]. These revised levels of evidence have been simplified when compared with the previous version; they were designed with the specific aim of providing support for clinicians for heuristic decision making thus ideally suiting the purpose of this publication. However, the initial sentence of the accompanying introductory document should always be kept in mind when interpreting these recommendations: ‘No evidence ranking system or decision tool can be used without a healthy dose of judgment and thought.’ [14].

## 4. Staging

Staging of MF/SS is based on a tumour–node–metastasis (TNM) classification system originally devised in 1979 [15]. A revision and expansion that also includes blood involvement (TNMB) has been published in 2007 and is used here for stratification of treatment recommendations [16]. Recent studies have supported the prognostic relevance of these newly refined stages (Tables 3) [17–20]. Additionally, histological findings

Table 2  
Detail from: Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence [13].

Question: Does this intervention help?	Level <sup>a</sup>
Systematic review of randomised trials or <i>n</i> -of-1 trials	1
Randomized trial or observational study with dramatic effect	2
Non-randomized controlled cohort/follow-up study <sup>b</sup>	3
Case series, case–control studies, or historically controlled studies <sup>b</sup>	4
Mechanism-based reasoning	5

<sup>a</sup> Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

<sup>b</sup> As always, a systematic review is generally better than an individual study.

Table 3a  
TNMB staging for mycosis fungoides and Sézary syndrome [16].

### Skin

- T1 Limited patches, papules, and/or plaques covering <10% of the skin surface. May further stratify into T1a (patch only) versus T1b (plaque ± patch).  
 T2 Patches, papules, or plaques covering ≥10% of the skin surface. May further stratify into T2a (patch only) versus T2b (plaque ± patch).  
 T3 One or more tumours (≥1-cm diameter)  
 T4 Confluence of erythema covering ≥80% body surface area

### Node [181,182]

- N0 No clinically abnormal peripheral lymph nodes; biopsy not required  
 N1 Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1 or NCI LN<sub>0-2</sub>  
   N1a Clone negative  
   N1b Clone positive  
 N2 Clinically abnormal peripheral lymph nodes; histopathology Dutch grade 2 or NCI LN<sub>3</sub>  
   N2a Clone negative  
   N2b Clone positive  
 N3 Clinically abnormal peripheral lymph nodes; histopathology Dutch grades 3–4 or NCI LN<sub>4</sub>; clone positive or negative  
 Nx Clinically abnormal peripheral lymph nodes; no histologic confirmation

### Visceral

- M0 No visceral organ involvement  
 M1 Visceral involvement (must have pathology confirmation and organ involved should be specified)

### Blood

- B0 Absence of significant blood involvement: ≤5% of peripheral blood lymphocytes are atypical (Sézary) cells  
   B0a Clone negative  
   B0b Clone positive  
 B1 Low blood tumour burden: >5% of peripheral blood lymphocytes are atypical (Sézary) cells but does not meet the criteria of B2  
   B1a Clone negative  
   B1b Clone positive  
 B2 High blood tumour burden: ≥1000/μL Sézary cells with positive clone

SS is staged as T4 N2/3/x M0 B2.

that might be of prognostic importance but which are not accounted for by the TNMB classification are the infiltration of hair follicles (folliculotropism) and a finding of >25% of large cells in the dermal infiltrate (large cell transformation) [16].

## 5. Management options and treatment modalities considered for inclusion in the consensus recommendations

In the following paragraphs a short description and literature review of the various management options and treatment modalities for MF/SS is provided. It should be noted that the list is not comprehensive as it does not include experimental treatments and modalities for which only minor literature support exists. Special emphasis is given to treatments that are available and commonly used in Europe.

### 5.1. Expectant policy (watch and wait)

Patients with stage IA disease have a low risk of progression, which has been estimated to be 10% within 10 years, and a life expectancy that appears to be very similar to that of an age and sex matched population [20–22]. Thus the previously reached consensus is again confirmed here to include ‘Expectant Policy’ as a legitimate management option for patients with MF stage IA. However, this strategy must incorporate careful monitoring and patient education as a few patients, who currently cannot be identified with certainty in advance, will eventually experience progression in their disease. The influence of skin-directed therapy (SDT) on the prevention of progression is not fully established. Although reliable predictive biomarkers for progression in MF are lacking there is evidence supporting that the subdivision of IA and IB stages according to clinical presentation into patch (T1/2a) and plaque (T1/2b) disease might well be of prognostic significance [16–18,20,23]. It is thus recommended to offer a ‘watch and wait’ expectant policy only to informed T1a patients.

### 5.2. Skin-directed therapy

#### 5.2.1. Topical corticosteroids

Although only a single study exists on the use of topical corticosteroids in MF, this therapy is widely used and is commonly considered to be useful for palliation in the treatment of individual lesions in early patch/plaque disease [24]. In an uncontrolled study, Zackheim *et al.* prospectively evaluated the twice-daily use of mainly high-potency topical corticosteroids (clobetasol propionate in 85% of patients) in 79 patients with stage IA/B disease and observed an overall response rate of 94% [25]. As no further published evidence exists, no other advice can be given other than to assign preference to high potency over less potent topical steroids. Toxicity is

Table 3b  
Clinical stages (5-year disease free survival (DSS) according to [17]).

Stage	T	N	M	B	5-year DSS (%)
IA	1	0	0	0.1	98
IB	2	0	0	0.1	89
IIA	1.2	1.2	0	0.1	89
IIB	3	0–2	0	0.1	56
IIIA	4	0–2	0	0	54
IIIB	4	0–2	0	1	48
IVA1	1–4	0–2	0	2	41
IVA2	1–4	3	0	0–2	23
IVB	1–4	0–3	1	0–2	18



negligible if the precautions usually associated with the use of these topical agents in chronic skin conditions are followed.

### 5.2.2. Topical mechlorethamine (HN2)

Mechlorethamine is an alkylating agent that received its initial approval in the United States of America (USA) for the topical treatment of MF in 1949. It is only recently that based on the results of a pivotal phase II study a commercial 0.02% gel preparation was approved by the US Food and Drug Administration (FDA) for the treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy [26–28]. Two-hundred sixty patients with MF stage IA–IIA who had not used topical mechlorethamine within 2 years and were naïve to treatment with topical carmustine were included in the pivotal study and randomly allocated to the commercial gel preparation or a 0.02% compounded mechlorethamine ointment. The 0.02% gel proved non-inferior to the ointment (response rates 58.5% versus 47.7%, respectively) with a significantly shorter time-to-response. No drug-related serious adverse events occurred within a duration of treatment of up to 12 months. However, more than 50% of patients in both groups experienced skin-related adverse events, most commonly irritant contact dermatitis leading to withdrawal in 20.3% and 17.3% of patients (gel versus ointment, respectively) [27]. The gel should be applied once daily to all affected areas of the skin. The product has recently been granted marketing authorization in Europe as an orphan medicinal product for the treatment of ‘mycosis fungoides-type cutaneous T-cell lymphoma’. According to published evidence and upon its availability it is recommended for first line treatment of early stage disease (stages IA–IIA).

A number of large, uncontrolled studies on the use of various compounded formulations of mechlorethamine have been reported, mostly from groups in the USA but including also a Danish cohort that show response rates of up to 83% depending on disease stage and no significant evidence for long-term toxicity or an increased rate of secondary cutaneous malignancies [9,29–31].

### 5.2.3. Topical bexarotene

Bexarotene is a retinoid that selectively binds and activates retinoid X receptors (‘rexinoid’). It is available for systemic therapy (see below) and in a 1% gel formulation for topical application. The gel is approved by the FDA for topical treatment of cutaneous lesions in patients with CTCL (Stage IA and IB) who have refractory or persistent disease after other therapies or who have not tolerated other therapies. The overall response rates reported from two prospective trials are between 44% and 63% depending on study end-point definition with a time to response between 28 and 504 days [32,33].

Toxicity is mild and mainly restricted to skin irritation. Like other retinoids, bexarotene is teratogenic and is thus contraindicated in pregnancy and requires special precautions in women of childbearing potential and male partners thereof. The product is not approved in Europe and no recommendation as to its use will thus be included in the current consensus.

### 5.2.4. Ultraviolet (UV) phototherapy

8-Methoxypsoralen plus ultraviolet A (UVA) (320–400 nm, PUVA) and ultraviolet B (UVB), either broadband (290–320 nm, bbUVB) or narrow band (311–312 nm, nbUVB), have a longstanding history in the treatment of MF with a large number of patients reported in retrospective and prospective cohorts. Other emerging variants of UV-phototherapy include excimer sources (308 nm) and UVA1 (340–400 nm) [34]. Only PUVA and UVB will be included into the options recommended here as only these are widely available, accessible to many patients and supported by ample evidence. Recent reviews on the topic have been published including a comprehensive consensus statement from the United States Cutaneous Lymphoma Consortium [34–36], which provide an excellent overview on the pertinent data.

In clinical practice today, broadband ultraviolet B (bbUVB) has become inaccessible to most patients as sources emitting bbUVB have mostly been replaced by narrow band ultraviolet B (nbUVB) lamps, which have been developed by van Weelden as a less erythemogenic and more effective treatment for psoriasis [35,37]. Similarly, there seems to be no disadvantage in the treatment of MF, as the efficacy of nbUVB to induce remissions in early MF, demonstrated initially in 1999, was subsequently confirmed in a number of studies without any evidence of inferiority compared with bbUVB [38,39]. This together with other practical advantages make nbUVB a primary option for the treatment of early MF, particularly stages T1a and T2a, which are characterised by patches only. For plaque disease (T1b, T2b) and for patients with dark skin PUVA is still recommended. This is not only due to mechanistic reasoning (UVA is able to penetrate deeper into the dermis than UVB and thus should theoretically be more effective for the treatment of thick lesions) but also to the large body of evidence that has accumulated since the first report of the successful use of PUVA for MF in 1976 and to the lack of prospective studies comparing nbUVB to PUVA [34,40].

Technically, phototherapy in MF is prescribed and applied in analogy to what is established and routinely used for the treatment of psoriasis. PUVA is usually done with 8-methoxypsoralen supplied orally. Although bath PUVA with 8-methoxypsoralen has been shown in a small retrospective analysis to be effective, its use is not generally recommended because with bath PUVA

the head is usually not exposed to the photosensitiser and might be a site of early relapse [41,42]. Although evidence is anecdotic, cream PUVA, where 8-methoxypsoralen is only applied to the disease site, may be used for unilesional disease and pagetoid reticulosis [43].

Upon insufficient response or immediate relapse phototherapy can be combined with systemic therapies, most commonly retinoids or interferon  $\alpha$  (IFN- $\alpha$ ) (see below). Another widely used practice to prevent relapses or to maintain responses is to continue therapy for prolonged periods after complete or almost complete responses have been achieved (maintenance therapy, see below).

An important issue relating to phototherapy of MF is long-term toxicity, particularly as the major target population, namely patients with early stages might have a normal or almost normal life expectancy. For patients with psoriasis an increased risk of squamous cell carcinoma associated with PUVA has been well defined from a large prospective cohort study whereas for UVB less thoroughly performed studies could not show an increased cancer risk [44,45]. For patients with MF, similar studies have not been done, and their risk of skin cancer associated with phototherapy is unknown.

#### 5.2.5. Total skin electron beam therapy

In total skin electron beam (TSEB) therapy, electrons, generated in a linear accelerator, are attenuated to penetrate the skin to a limited depth. Thus toxicity to internal organs including the bone marrow is largely avoided. The technique has a long history in the treatment of cutaneous lymphomas and already in 1961 a nine-year follow up of 200 patients was reported [46]. Since then, not only radiation technology has advanced but also clinical experience from large centres has helped to refine the method to provide a sufficiently distributed dose to the target volume to reliably induce remission with acceptable toxicity. Based on evidence from retrospective studies, which have been extensively reviewed, a standard treatment course consisting of a total dose of 30–36 Gy applied over a period of 8–10 weeks is able to induce high remission rates, particularly in T2 and T3 disease. In selected patients with relapse after good initial response treatment has been successfully repeated without significant additional toxicity. TSEB can be combined with nodal and localised skin irradiation [47,48].

Consensus guidelines on the use of TSEB in MF have been published [49–52]. However, toxicity of TSEB is dose-related and the recommended dose as mentioned above is based on experience and theoretic reasoning rather than on comparative trials. More recently, low-dose regimens (in the range of 10–12 Gy) have been investigated for their clinical efficacy. No direct comparisons with standard dose TSEB exist and it is currently unknown whether low-dose regimens with

their associated lower toxicity, shorter treatment times (2–3 weeks) and the additional advantage of allowing multiple re-treatments, will be equally effective in inducing remissions [53–57].

#### 5.2.6. Localised radiotherapy

Localised, superficial radiotherapy provides effective palliative treatment for individual lesions and may even induce long-term remission in unilesional disease. Photons as well as electron beam have been used and doses have ranged from 0.7 to 35 Gy and may be fractionated [54,58–60]. In one study brachytherapy was successfully used for facial lesions [61]. Localised radiotherapy can be either used alone (particularly in unilesional MF and pagetoid reticulosis) or in combination with systemic or other skin directed therapies. For unilesional MF and pagetoid reticulosis a dose of 20–24 Gy is advised [57]. In patients with more advanced disease isolated plaques or tumours can be treated for effective palliation with low-doses ( $2 \times 4$  Gy) [62].

### 5.3. Systemic therapies

#### 5.3.1. Retinoids (incl. bexarotene)

Retinoids are derivatives of vitamin A. All-trans retinoic acid, isotretinoin, etretinate, acitretin and — more recently — bexarotene and alitretinoin have been used for the treatment of cutaneous T-cell lymphomas alone or in combination since the early 1980s [63–65]. Among these bexarotene stands out through its specific binding to the retinoid-X-receptor (thus termed a ‘rexinoid’); it is the only member of the group that was specifically developed and has received approval for the treatment of CTCL [66–69]. According to its label, bexarotene is indicated for the treatment of cutaneous manifestations of advanced stage CTCL in patients who are refractory to at least one prior systemic therapy with a reported overall response rate of 45% [70]. In clinical practice, bexarotene has been used as primary systemic therapy and has shown efficacy also in extracutaneous involvement [68,71,72]. The other most commonly used although not approved and less thoroughly studied retinoids are acitretin (which has replaced its prodrug etretinate in the 1990s) and isotretinoin [64]. Due to heterogeneity of the published evidence and since no direct comparisons exist no conclusion as to superiority in clinical efficacy of one substance over the other can be made.

Retinoids are generally well tolerated and share a common adverse effect profile with variable individual symptoms depending on the substance used. Most commonly observed are drying of the skin and mucous membranes, elevated blood lipids, and in the case of bexarotene central hypothyroidism requiring thyroid hormone substitution in most patients [73]. All retinoids are teratogenic.

With retinoids as monotherapy moderate response rates can be achieved in MF/SS, the substances thus are commonly used in combination (see below) or in maintenance (see below) since they appear safe with long-term use.

### 5.3.2. Interferon (IFN)- $\alpha$

Three types of recombinant interferons (IFN- $\alpha$ , IFN- $\beta$ , IFN- $\gamma$ ) are currently available for therapeutic use with IFN- $\alpha$  existing also in a pegylated form. Therapeutic activity of IFN- $\alpha$  in CTCL was initially reported by Bunn *et al.*, in 1984 [74]. The same author some years later summarised the then pertinent evidence and concluded that all of the recombinant IFNs are active for the treatment of MF and SS [75]. However, only recombinant IFN- $\alpha$  has been studied in more detail, has received approval for the treatment of CTCL and remains the most widely used IFN in the treatment of MF/SS [76]. Various treatment and dose escalation schedules have been used with individual doses ranging from 3 million units (MU) to 18 MU applied subcutaneously either three times per week or daily. A commonly used regimen is to start with 3 MU three times weekly with dose escalation upon insufficient response and tapering for maintenance. Side-effects are dose dependent and include flu-like symptoms, elevated transaminases, leukopenia, thrombocytopaenia, and – probably under-recognized mental depression, cardiac arrhythmias, and thyroid dysfunction [76,77]. Similar to the literature on the older retinoids (with the exception of bexarotene, see above), published evidence on the clinical efficacy of IFN- $\alpha$  suffers from heterogeneity in treatment schedule, patient selection, and methodology. Thus, reported overall response rates range from 0 to 80% without a clear correlation between dose and response [76].

### 5.3.3. IFN- $\alpha$ combined with retinoids

Reports on the combined use of IFN- $\alpha$  and retinoids appeared beginning from the late 1980s [78–81]. Etretnate or isotretinoin have been used in these small heterogenous studies, which showed that the combination is tolerable without unexpected toxicity and is able to induce and maintain clinical responses. In the prospective randomised study by Stadler *et al.* acitretin was used in combination with IFN- $\alpha$  and compared with the IFN- $\alpha$  – PUVA combination in 82 patients with early stage MF [82]. Although overall response rates did not differ between treatment groups (90.5% versus 90%, respectively) the rate of CR was higher with IFN- $\alpha$ /PUVA (70%) compared with the acitretin combination (38%). The study clearly shows that IFN- $\alpha$  plus PUVA is superior to IFN- $\alpha$  plus acitretin in terms of time to remission and CR rate. However, its results should not be interpreted as an argument to dismiss the latter combination since its efficacy, shown in earlier less stringent trials, was confirmed and it fulfils a need for

combination therapy in patients insufficiently responding to monotherapy when access to PUVA is limited. More recently the combination of tretinoin (all-trans retinoic acid) with IFN- $\alpha$  has been compared with IFN- $\alpha$  combined with low-dose methotrexate in an open prospective non-randomised trial [83]. Reportedly, both regimens were of similar efficacy and toxicity. In another small trial IFN- $\alpha$  was added to bexarotene upon incomplete remission after 8 weeks with no apparent benefit of the combination [84]. Taken together, the accumulated evidence confirms the clinical applicability of IFN- $\alpha$  – retinoid combinations in MF. At the same time it fails to demonstrate the superiority of any retinoid over the other and of the various combination regimens over monotherapy. Thus a combination of IFN- $\alpha$  and retinoids is recommended when monotherapy with either substance has failed and when the IFN- $\alpha$  – PUVA combination is contraindicated or unavailable.

### 5.3.4. IFN- $\alpha$ or retinoids combined with SDT

The combination of PUVA with systemic retinoids was initially developed to improve efficacy and reduce potential side-effects of photochemotherapy in the treatment of psoriasis [85]. Subsequently, the concept was carried over to CTCL and investigated in a small series of uncontrolled studies and case collections [86–88]. Etretnate and acitretin were used in these studies from which no conclusion as to superiority of the combination over phototherapy alone can be made. With the systematic development and regulatory approval of bexarotene for the treatment of CTCL interest in the combination of this substance with phototherapy led to the publication of a number of reports [89–93]. Outstanding among these studies is a randomised phase III trial conducted by the EORTC Cutaneous Lymphoma Task Force where bexarotene combined with PUVA was compared to PUVA alone in early stage (IB–IIA) MF. The study was closed prematurely due to low accrual and thus did not reach its primary end-point (overall response rate). However, while confirming the safety of the combination its results indicate no significant difference in response rate and response duration between treatments [91].

The first small study about the use of combining IFN- $\alpha$  and PUVA for the treatment of CTCL appeared in 1990 and described complete remission in 12 out of a total of 15 patients [94]. A number of further small studies and case series followed [95–100] using various IFN- $\alpha$  dose schedules and PUVA regimens. Taken together these reports demonstrate that no increase in toxicity occurs with the combination but leave open the question whether it is more effective compared to monotherapy. Safety and efficacy IFN- $\alpha$  plus PUVA were confirmed by the above mentioned prospective trial [82] leaving, however, the issue of superiority compared to either monotherapy unresolved.



Other SDT that can be combined with systemic treatments are topical corticosteroids, nbUVB and localised radiotherapy (see above). Although not systematically studied these options are used based on institutional and personal experience and might prove useful on an individual basis.

In summary, current evidence does not support the use of combinations of SDT with systemic therapies as first line option in early stages of MF. However, when systemic therapy is indicated in more advanced stages adding on of an effective SDT might shorten time to response and alleviate symptoms more quickly and effectively.

### 5.3.5. Chemotherapy

*Conventional single agent and combination chemotherapy* have been used for the treatment of non-Hodgkin lymphoma since the 1970s with the (C)yclophosphamide-(H)ydroxydaunorubicin-(O)ncovin-(P)rednisone or (P)rednisolone [CHOP] regimen evolving as a long-standing standard option for aggressive disease. At the same time this and a number of other combinations and single agents have been tried in CTCL with variable, but generally short-lived success. A comprehensive review on these early experiences is published elsewhere [101]. Already in 1989, the results of a seminal prospective randomised trial comparing early aggressive with stage-adapted therapy restricted (poly-) chemotherapy to patients with advanced disease, a restriction still applying today [8]. In the meantime novel chemotherapeutic agents with activity in MF and SS have been developed. Among these promising results with acceptable toxicity have been obtained with pegylated liposomal doxorubicin [102–107] and gemcitabine [108–112]. Treatment regimens in these studies largely followed established dosage recommendations as described for their approved indications. In an EORTC-sponsored prospective multicentre trial Dummer *et al.* could demonstrate an acceptable safety profile and an overall response rate of 40.8% in 49 patients with pre-treated ( $\geq 2$  previous therapies) advanced stage (IIB, IVA, or IVB) MF using pegylated liposomal doxorubicin at 20 mg/m<sup>2</sup> biweekly. Median duration of response was 6 months, similar to what has been reported for other chemotherapy regimens in this high risk population [106]. Gemcitabine was also investigated in combination with bexarotene in a phase II protocol resulting in poor response rates and increased toxicity compared to the single agents leading to the conclusion that this combination should be avoided [113]. A number of other cytotoxic agents have been tried in CTCL including the purine analogues (deoxycoformycin, 2-chlorodeoxyadenosine, fludarabine), bendamustine and others [114–119]. However, limited published evidence precludes inclusion of these substances in the present recommendations.

Two other chemotherapeutic agents are included in these recommendations and thus will be mentioned briefly:

*Chlorambucil* is an alkylating agent that was developed in the 1950s for the treatment of chronic lymphocytic leukaemia and non-Hodgkin lymphomas [120]. It can be administered by mouth. In combination with low dose prednisone it was introduced for the treatment of SS in the 1970s by Winkelmann [121,122]. The original regimen consists of continuous treatment with 2–6 mg/day of chlorambucil and prednisone at an initial dose of 20 mg/day to be tapered to 0–10 mg/day. Although more recently a variant with intermittent dosing was described in a small patient series to be as effective as the original regimen the original prescription is still recommended [123]. However, since in addition to myelosuppression prolonged exposure to chlorambucil carries a leukemogenic risk long-term continuous use should be avoided [124].

*Methotrexate* was developed as a cytotoxic antifolate in the wake of the 1950s breakthrough of anticancer chemotherapy for the treatment of childhood leukaemias [125]. Soon afterwards its usefulness for treatment of psoriasis and rheumatoid arthritis was demonstrated and low-dose once-weekly methotrexate has become a well-tolerated, standard treatment for non-oncological conditions [126]. There are only few studies on the use of methotrexate in various dosing for the treatment of MF/SS that have been reviewed earlier [9]. Since then additional experience on the safe combination of methotrexate with bexarotene and IFN- $\alpha$ , respectively, have been published [83,127]. No conclusion, however, as to the superiority of these combinations over monotherapy is possible and no recommendation as to the optimal use of these regimens can be made. In the context of this consensus the recommended dose of methotrexate is 5–25 mg once weekly.

### 5.3.6. Targeted immunotherapy

Since the introduction of monoclonal antibodies into cancer therapy in the 1990s a number of recombinant immunoglobulins and other protein constructs have also been developed for and tried in non-Hodgkin lymphomas, with rituximab as a most remarkable example of success in B-cell lymphomas [128]. Some agents have also demonstrated activity in CTCL and it is to be expected that in the near future new antibodies and antibody-constructs will enter the clinics [129].

*Denileukin diftitox* was developed for the treatment of CTCL and became the first fusion toxin to be approved. It is a recombinant protein consisting of interleukin (IL)-2 linked to the catalytic domain of diphtheria toxin genetically engineered with the intention to target cells expressing the IL-2 receptor [130]. Its activity in the treatment of CTCL has been demonstrated in two phase III trials with overall response rates of 30% and 44% and an acceptable safety profile although grade 3 and 4

capillary leak syndrome was observed in 4% of patients [131,132]. Since denileukin diftitox is currently unavailable and did not obtain marketing authorisation in Europe its use is not included in these consensus recommendations.

*Alemtuzumab* is a humanised recombinant IgG1 monoclonal antibody against the CD52 cell surface glycoprotein, which is expressed on normal and malignant B and T lymphocytes but not on haematopoietic progenitors. Alemtuzumab was initially developed and approved for the treatment of lymphoid malignancies. More recently its immunosuppressive effects have been utilised to successfully treat multiple sclerosis [133,134]. Although alemtuzumab is currently commercialised only for multiple sclerosis it is still available for the treatment of lymphoid neoplasms through a special access programme. Overall response rates of more than 50% have been obtained in MF/SS using the standard dose of 30 mg intravenous (i.v.), three times weekly. At this dosage immunosuppression and opportunistic infections are the most common, sometimes severe adverse events [135–137]. From these studies and a recent long-term observation it appears that alemtuzumab is effective primarily in patients with erythroderma (T4) and blood involvement ( $B \geq 1$ ) and may be able to induce long-term remissions in selected patients [138]. With the intention to reduce toxicity while maintaining efficacy low dose regimens have been introduced [139–141]. Doses up to 15 mg s.c. every other day were used and in small patient series response rates similar to those reported from earlier studies were observed without relevant infectious complications when single doses did not exceed 10 mg.

*Brentuximab vedotin* is an antibody-drug conjugate consisting of an anti-CD30 IgG1 antibody attached to monomethyl auristatin E, a microtubule-disrupting agent, through a protease-cleavable linker [142]. Upon internalisation into CD30 expressing cells the linker is cleaved and monomethyl auristatin E released into the cell to induce cell cycle arrest. The drug is currently approved in Europe and the USA for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL), patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplantation, and adult patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL). The safety and efficacy of brentuximab vedotin in CTCL has been investigated in two phases II and one very recently reported phase III trials [143–145]. In one of these studies 32 patients with MF/SS and any level of CD30 expression were included. An overall response rate of 70% observed in patients with a wide range of CD30 expression and a lower likelihood of response if CD30 was expressed in less than 5% of cells as assessed by immunohistochemistry [144]. In the other study 48 patients with CD30+ CTCL (incl. lymphomatoid papulosis, primary cutaneous anaplastic

large cell lymphoma, and CD30+ MF/SS) were included with an overall response rate of 73% in the total study population and of 54% in patients with MF/SS ( $n = 28$ ). The main toxicities consisted of peripheral neuropathy, that can be dose-limiting, severe, and long-lasting, neutropenia, that can be severe; fatigue, nausea and alopecia. First results of a randomised, controlled phase III trial comparing brentuximab vedotin to physician's choice of methotrexate or bexarotene in pre-treated CD30+ CTCL have been recently reported [145]. In the intention-to-treat population of 128 patients highly significant improvements in the rate of overall responses lasting  $\geq 4$  months (56% versus 13%) and progression free survival (16.7 versus 3.5 months) were observed with brentuximab vedotin. Reported observed adverse events appear consistent with the reported safety profile of brentuximab vedotin. As at the date of writing brentuximab vedotin is not approved for the treatment of patients with MF/SS its use is not recommended in this consensus. However, based on the above mentioned level 2 evidence and since the drug is widely available in Europe it may be used on an individual basis upon physician's decision in advanced CD30+ cases.

*Mogamulizumab* is a humanized monoclonal antibody targeting the CC chemokine receptor 4 (CCR4) expressed on tumour cells of adult T-cell leukaemia-lymphoma (ATLL) and other T-cell lymphomas. The antibody is modified in the composition of its carbohydrates ('glyco-engineered') to enhance its antibody-dependent cell-mediated cytotoxic (ADCC) activity [146]. Currently the drug is approved in Japan for relapsed or refractory CCR4+ peripheral T-cell lymphoma and CTCL. In 3 early phase studies a total population of 48 patients with relapsed CCR4+ CTCL, pre-treated MF and SS were treated with mogamulizumab with overall response rates between 38% and 29% mainly in leukaemic CTCL variants. Reported side-effects were mostly low grade and included chills, fever, rash, nausea, headache and infusion-related reactions [147–149]. Thus, although promising, the published evidence on the efficacy of mogamulizumab in the treatment of MF/SS is sparse and the results of an ongoing randomised phase III trial against vorinostat in pre-treated CTCL (NCT01728805) have to be awaited before further recommendations can be made.

### 5.3.7. Extracorporeal photochemotherapy

Extracorporeal photochemotherapy (ECP; which has also been variously called photopheresis, extracorporeal photopheresis, or extracorporeal photoimmunotherapy) is a form of phototherapy where blood is exposed extracorporeally to the photoactivated drug 8-methoxypsoralen (8-MOP). The use of ECP was first reported in 1987 by Edelson *et al.* in CTCL for which it is approved in Europe and the US [150]. Other indications where ECP is used include systemic sclerosis, graft-versus-host disease, solid organ transplant

rejection, and Crohn's disease [151]. ECP has an excellent safety profile with almost absent adverse events and details on the recommended prescription, schedule, and other practical issues have been recently published elsewhere [152]. Since the original publication by Edelson *et al.* who reported a response rate of 73% (with most of the patients having T4 disease) a number of case series and retrospective studies confirming the efficacy of photopheresis particularly in patients with erythrodermic MF and SS have been published with response rates around 60% [153]. Remarkably in most of these reports ECP was used in combination with other agents and modalities, including retinoids, interferons, PUVA, and others, demonstrating on the one hand that ECP can be safely combined with many other agents available for the treatment of MF/SS, and leaving open, on the other hand, the question of superiority of any combination over the other and over monotherapy.

#### 5.3.8. Haematopoietic stem cell transplantation

The first transfer of haematopoietic stem cells from allogeneic bone marrow to terminally ill patients was published in 1957 by E. Donnall Thomas who was awarded the Nobel Prize for his achievements in 1990 [154]. In the meantime the technique has been refined through advances in immunological understanding and with the development of efficient protocols for stem cell collection from peripheral and umbilical cord blood, conditioning and support of engraftment after transplantation. Major indications today still include haematological malignancies but have been extended to hereditary bone marrow disease such as thalassaemia and sickle cell anaemia. The first report on autologous stem cell transplantation (ASCT) after total body irradiation in MF appeared in 1991 and described complete remission in five out of six patients with early relapse in three of the responders [155]. Other small case series confirmed that although aggressive treatment with ASCT rescue is feasible and able to induce remissions almost all patients will eventually relapse [156]. Consequently this approach has been abandoned in MF/SS and is not recommended in this consensus. With allogeneic stem cell transplantation (alloSCT) on the other hand durable remissions have been achieved in CTCL and (with the exception of localised radiotherapy for unilesional MF) remains the only treatment option in MF/SS with curative intention. The published evidence from retrospective studies and case series on alloSCT in CTCL comprises nine studies on a total of approximately 250 patients [157–165]. A comprehensive summary and review has been published recently [156]. Both, myeloablative and reduced-intensity conditioning have been used with similar efficacy and lower complication rates including reduced non-relapse mortality (NRM) and lower rates of chronic graft versus host disease (GvHD) in the latter. Graft versus lymphoma (GvL) effect appears to be important for induction and

maintenance of remission and donor lymphocyte infusions and tapering of immunosuppression have been demonstrated to induce secondary remission. In the study with the longest reported observation time overall survival was 46% and 44% at 5 and 7 years after transplant, respectively, with 22% NRM [165]. In summary, alloSCT – particularly using reduced-intensity conditioning – is able to induce long-term remissions in a substantial percentage of patients with MF/SS although at the price of a high rate of treatment related morbidity and mortality. Consequently, patient selection is difficult, requires careful counseling and should focus mainly on younger, well performing patients suffering from advanced stages of the disease, with a low tumour burden at the time of transplantation and at the same time a high predictable risk of progression and poor prognosis.

#### 5.3.9. Histone deacetylase inhibitors

Histone deacetylases (HDAC) are a class of ubiquitously expressed enzymes, that catalyse the removal of acetyl groups from histones and by this are key regulators of epigenetic regulation of transcription. Specific pharmacological inhibitors of HDAC have been developed and investigated in preclinical and clinical studies for their potential as novel antitumour agents that work through modification of the epigenetic aberrations associated with cancer [166]. Based on the results of pivotal trials three substances, vorinostat, romidepsin, and belinostat are currently approved by the FDA for 'treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies' (vorinostat); 'treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy' and 'treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy' (romidepsin); and for 'treatment of patients with relapsed or refractory peripheral T-cell lymphoma' (belinostat) [167–172]. Efficacy and toxicity of these substances are similar with a reported overall response rate of about 30% and class-as well as substance specific toxicities, most notably gastrointestinal side-effects, thrombocytopenia, QTc prolongation, and deep vein thrombosis with vorinostat. New substances are in development and the clinical efficacy and toxicity of HDAC inhibitors in CTCL have been recently reviewed elsewhere [173]. Since currently none of these drugs has obtained approval in Europe HDAC inhibitors will not be considered in these consensus recommendations.

#### 5.4. Maintenance

MF/SS are chronic conditions that are generally considered incurable with the main aim of treatment in achieving effective palliation, i.e. remission of symptoms

with improvement or at least maintenance of quality of life. The exceptions mentioned above are alloSCT and radiotherapy of unilocalised disease where long-term remissions have been observed and treatment is prescribed with the intention to cure. All other treatment strategies have a variable potential to achieve remissions in appropriately selected patients. However, almost all patients will eventually experience relapse or progression either during ongoing treatment or after its cessation [174]. In this context maintenance therapy can be defined as a continuous exposure to a skin directed or systemic therapy once remission has been achieved with the aim to maintain response and prevent relapse and progression. As a consequence to qualify for the use as maintenance modalities treatments must be selected to be effective, palliative, available, and easy to apply, i.e. have an excellent safety profile and not or only minimally interfering with quality of life. These criteria are largely fulfilled by a number of treatment options mentioned in this report (Table 9) and some of them are widely used in clinical practice, although without supportive evidence, e.g. PUVA [35,175]. Practically, maintenance can be performed with tapering of the remission-inducing treatment as is commonly done with phototherapy, retinoids, IFN- $\alpha$ , ECP, and others or with the introduction of a maintaining treatment after remission has been achieved with a method that has dose-limiting toxicity, e.g. TSEB and systemic chemotherapy. As no guiding evidence exists on the indication and selection of maintenance in MF/SS decisions should be considered mainly in patients  $\geq$ IB (T2b) with high risk of relapse and/or progression after consideration of the prerequisites described above and careful counseling.

## 6. Treatment recommendations by disease stage

Stagewise consensus recommendations for the selection of a treatment are laid out in Tables 4–8, subdivided

Table 4a  
Recommendations for first-line treatment of MF stages IA, IB, and IIA.

Expectant policy (mainly T1a)	Level 4
SDT	Level 3
Topical corticosteroids (mainly T1a and T2a)	
UVB <sup>a</sup> (mainly T1a and T2a)	Level 2
PUVA <sup>b</sup>	Level 2
Localised RT (for localised MF including pagetoid reticulosis)	Level 4
Mechlorethamine <sup>c</sup>	Level 2

<sup>a</sup> See text for details on recommended light sources.

<sup>b</sup> See text for details on recommendations as to the use of oral, topical, and bath PUVA.

<sup>c</sup> Most of the evidence was obtained using compounded formulations; a commercial product is available in the US with marketing authorisation pending in Europe (see text for further details).

Table 4b  
Recommendations for second-line treatment of MF stages IA, IB, and IIA.

Systemic therapies <sup>a</sup>	
Retinoids <sup>b</sup>	Level 2
IFN- $\alpha$	Level 2
TSEB (mainly T2b)	Level 2
Low-dose MTX	Level 4

<sup>a</sup> The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.

<sup>b</sup> Including RAR and RXR agonists.

Table 5a  
Recommendations for first-line treatment of MF stage IIB.

Systemic therapies <sup>a</sup>	
Retinoids <sup>b</sup>	Level 2
IFN- $\alpha$	Level 2
TSEB	Level 2
Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)	Level 4
Low dose MTX	Level 4
Localised RT <sup>c</sup>	Level 4

<sup>a</sup> The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.

<sup>b</sup> Including RAR and RXR agonists.

<sup>c</sup> Used as add-on treatment in combination with systemic and other skin directed therapies.

Table 5b  
Recommendations for second-line treatment of MF stage IIB.

Polychemotherapy <sup>a</sup>	level 3
Allogeneic stem cell transplantation <sup>b</sup>	level 3

<sup>a</sup> CHOP is the most widely used regimen with a number of variants and other combinations available.

<sup>b</sup> Should be restricted to exceptional patients, see text for details.

Table 6a  
Recommendations for first-line treatment of MF stage IIIA and B.

Systemic therapies <sup>a</sup>	
Retinoids <sup>b</sup>	Level 2
IFN- $\alpha$	Level 2
ECP <sup>c</sup>	Level 3
Low dose MTX	Level 4
TSEB	Level 2

<sup>a</sup> The following agents are most commonly combined with PUVA, combinations with other modalities and with each other are also widely used.

<sup>b</sup> Including RAR and RXR agonists.

<sup>c</sup> ECP can be used alone or in combination with skin directed and other systemic therapies.

Table 6b  
Recommendations for second-line treatment of MF stage IIIA and B.

Monochemotherapy (gemcitabine, pegylated liposomal doxorubicine)	Level 3
Allogeneic stem cell transplantation <sup>a</sup>	Level 3

<sup>a</sup> Should be restricted to exceptional patients, see text for details.



Table 7

Recommendations for treatment of MF stages IVA and IVB.<sup>a</sup>

Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy) <sup>b</sup>	Level 3
Radiotherapy (TSEB and localised) <sup>c</sup>	Level 4
Alemtuzumab (mainly in B2)	Level 4
Allogeneic stem cell transplantation	Level 3

<sup>a</sup> For treatment of MF stage IVA1 recommendations for SS (Table 8a and b) might apply.<sup>b</sup> Monochemotherapy should be preferentially used.<sup>c</sup> Used alone or in combination with systemic therapies.

Table 8a

Recommendations for first-line treatment of SS.

ECP <sup>a</sup>	Level 3
Chlorambucil + prednisone	Level 3
Systemic therapies in combination with ECP or PUVA	
Retinoids <sup>b</sup>	Level 3
IFN- $\alpha$	Level 3
Low dose MTX	Level 4

<sup>a</sup> ECP can be used alone or in combination with skin directed and other systemic therapies.<sup>b</sup> Including RAR and RXR agonists.

Table 8b

Recommendations for second-line treatment of SS.

Chemotherapy (gemcitabine, pegylated liposomal doxorubicine, CHOP and CHOP-like polychemotherapy)	Level 3
Alemtuzumab	Level 4
Allogeneic stem cell transplantation <sup>a</sup>	Level 3

<sup>a</sup> Should be restricted to exceptional patients, see text for details.

Table 9

Agents that can be used for maintenance after remission has been achieved in MF and SS.<sup>a</sup>

ECP
IFN- $\alpha$
Low-dose methotrexate
Mechlorethamine
PUVA
Retinoids
Topical corticosteroids
UVB

<sup>a</sup> Options are listed alphabetically and should be chosen to be effective, tolerable, easy to use, and efficient. OCEBM levels are generally 5.

into first- and second-line options, where second line options should be reserved for patients who are refractory or have contraindications to first line therapy. In this context a patient is considered refractory to a specific treatment if he shows no or only minimal response and upon progression under treatment. In case of relapse after a successful course of a first line

treatment patients should not be considered refractory and therapy can be reinitiated in most cases. As in the previous version of this report no division into first- and second-line options is made for stage IV disease as according to the opinion of the authors pertinent evidence as well as personal experience is insufficient to justify such a separation. The order of recommendations is based on the consensus opinion of the authors whenever possible. The individual choice of the appropriate therapy can differ and will depend on clinical presentation and treatment availability. Furthermore, in addition to clinical stage histological evidence of folliculotropism and large cell transformation can be associated with poorer outcome and more aggressive treatment might be considered [176–179].

## 7. Summary and conclusion

Following up on the initial report from the EORTC-CLTF on treatment of MF/SS we provide here a timely update based as before on a broad consensus among a representative group of experts from multiple European countries.

Although additional evidence has accumulated within the last 10 years, evidence levels supporting individual therapies are still low (with a few exceptions) and progress is gradual. The main changes regard treatment schedules and dosages (e.g. TSEB and alemtuzumab), more detailed specifications as to the preference of specific chemotherapeutic agents, and the inclusion of maintenance options and alloSCT and into the recommendations.

In general the principles on treatment selection in MF/SS as stated in the summary of the preceding version of this report still apply, namely that patients with early stage disease should primarily be treated with SDT and should they relapse to the skin receive further courses of the same or another SDT. Systemic therapy should be mainly considered for patients with advanced stages and for refractory cutaneous disease. Ideally, patients with advance-stage disease should have the option to enter multicentre clinical trials. Finally, as treatment of MF/SS is still palliative in almost all cases maintenance of quality of life should be at the centre of therapeutic strategies and be considered alongside response rates in clinical research.

## Disclaimer

These recommendations reflect the best data available at the time the article was prepared. Caution should be exercised in interpreting the data; the results of future studies may require alteration of the conclusions or recommendations in this report. It may be necessary or even desirable to depart from these recommendations in special circumstances. Just as adherence to guidelines

may not constitute defence against a claim of negligence, so deviation from them should not be necessarily deemed negligence.

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